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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,574	11/14/2003	Jeffrey M. Isner	47624-DVC (71417)	1777

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,574	ISNER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-61 and 63-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-61 and 63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 11/4/05 has been entered.

Amended claims 49-61 and 63-66 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The New Mater rejection is withdrawn in light of Applicant's amendment.

Priority

The instant claims are only entitled **at best to the effective filing date of 3/9/1999** because the provisional application 60/077,262, filed on 3/9/1998 does not have a written support for the administration of a stem cell factor (SCF) into any mammal or a concept for a co-administering any colony stimulating factor (CSF) other than a GM-CSF with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof.

Response to Argument

Applicant's argument related to the assigned priority date in the Amendment filed on 11/4/05 (page 7, fourth and fifth paragraphs) has been fully considered, but it is respectfully not found persuasive.

Applicant argues basically that the administration of GM-CSF prior to treatment of the ischemic tissue with DNA encoding angiogenic proteins can be found at least at

page 4, lines 4-6, and support for CSFs other than GM-CSF can be found in the description of the modification of GM-CSF protein can be found at least at page 6, lines 4-15.

Please note the instant claims recite "administering to the mammal an effective amount of at least one of: stem cell factor (SCF), colony stimulating factor (CSF) or an effective fragment thereof". Applicant has not pointed out which page number and which line number in the provisional application that has the written support for the administration of stem cell factor (SCF), or the concept of administering CSF factor other than GM-CSF that induces endothelial cell progenitor cell (EPC) mobilization and enhances neovascularization in ischemic tissue. Page 6, lines 4-15 still only concern with GM-CSF variants having equivalent functions and not any other colony stimulating factors as encompassed by the scope of the instant claims.

Claim Rejections - 35 USC § 103

Amended claims 49-61 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Hammond et al. (US Patent 5,880,090; IDS) for the same reasons already set forth in the Office Action mailed on 5/4/05 (pages 5-8).

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an

effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic protein includes aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner do not specifically teach the administration of an effective amount of a stem cell factor (SCF), a colony stimulating factor (CSF) or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, even though Isner

teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Hammond et al already teach that cytokines such as stem cell factor (SCF), granulocyte-macrophage conlony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering to the treated mammal an effective amount of at least one of SCF or CSF or an effective fragment thereof in light of the teachings of Hammond et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient; and this mobilization of endothelial cell

progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the therapeutic outcome. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Hammond et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicant's arguments related to the above rejection in the Amendment filed on 11/4/05 (page 8) have been fully considered, but they are respectfully not found persuasive.

Applicant argues basically that the Hammond reference provides methods for enhancing the endothelialization of a synthetic prosthetic vascular graft using certain cytokines such as G-CSF and GM-CS, and that the reference does not teach or suggest using the method to treat ischemic myocardial tissue, particularly along with injection of a nucleic acid encoding at least one angiogenic protein. Applicant also argues that Isner does not specify using SCF or CSF to treat myocardial ischemia. Applicant further argues that the Hammond reference is nothing more than an invitation to experiment with the circulating cells.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic protein includes aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells. Hammond et al already teach that cytokines such as stem cell factor (SCF), granulocyte-macrophage conlony-stimulating factor (GM-CSF),

granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37). As already noted in the previous rejection an ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the therapeutic outcome. Additionally, an ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Hammond et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Amended claims 49-61 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) for the same reasons already set forth in the Office Action mailed on 5/4/05 (pages 5-8).

The teachings of Isner have been presented above. However, Isner do not specifically teach the administration of an effective amount of a colony stimulating factor (CSF) or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, even though Isner teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, with recombinant G-CSF has angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see abstract and Methods).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by utilizing recombinant G-CSF as an endothelial cell mitogen to be administered to a patient in need thereof in light of the teachings of Bussolino et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Bussolino et al. already demonstrated that recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least

another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. This would in effect optimize the desired therapeutic outcome. The synergistic effects in the induction of angiogenesis would also be reasonably expected for the interaction between the administered G-CSF and encoded bFGF or its fragment being expressed from a delivered nucleic acid. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Bussolino et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicant's arguments related to the above rejection in the Amendment filed on 11/4/05 (pages 8-9) have been fully considered, but they are respectfully not found persuasive.

Applicant argues basically that the Bussolino reference teaches the use of particular CSFs to induce endothelial cells to proliferate and migrate *in vitro*, particularly in the rabbit cornea. The reference does not teach or suggest the use of the presently claimed invention to treat ischemic myocardial tissue.

Once again Applicant ignores completely the teachings of Isner used as the primary reference for the above 103 rejection. Please refer to the combined teachings

of Isner and Bussolino reference, the motivation for such a combination as well as a reasonable expectation of success in the rejection set forth above.

Double Patenting

Amended claims 49-61 and 63-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 52-56, 58-65 and 68 of copending Application No. 10/696,391 for the same reasons already set forth in the Office Action mailed on 5/4/05 (pages 10-12).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the Amendment filed on 11/4/05 (page 9), Applicant simply states that the provisional obviousness-type double patenting rejection will be addressed once there is indication of allowable subject matter. Please note that this response can be deemed to be Non-Responsive because Applicant does not indicate whether Applicant traverse with the rejection or a terminal disclaimer will be filed in the future. However, for the purpose of a compact prosecution, the rejection is maintained.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

CELIAN QIAN
PATENT EXAMINER